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A Novel Product from Beckmann Rearrangement of Erythromycin A 9(E)-oxime

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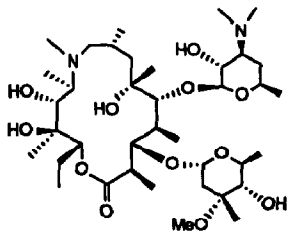
Abstract: Beckmann rearrangement of erythromycin A 9(E)-oxime with toluenesulfonyl chloride in ethyl ether at -45 °C generates 9,11-imino ether IV which leads to azithromycin. The 9,11-imino ether can also be readily obtained from isomerization of its isomer 6,9-imino ether III.

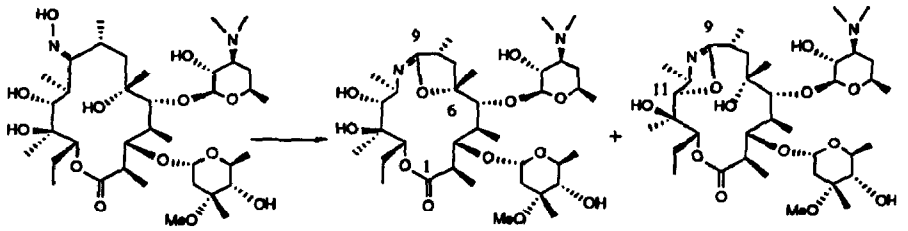
Azithromycin I is the first example of a new class of azalide antibiotics.[1] It differs structurally from erythromycin A by the insertion of a methyl-substituted nitrogen at position 9a in the lactone ring to create a 15-membered macrolide. This modification results in a significant improvement in potency against Gram-negative bacteria and distribution of high concentrations of drug into tissues.[2] The preparation of azithromycin is based on the Beckmann rearrangement of erythromycin A 9(E)-oxime **II** (Scheme 1). Intramolecular participation of the neighboring 6-hydroxy group is observed when the Beckmann rearrangement reaction is carried out at 0 °C with toluenesulfonyl chloride in aqueous-acetone, giving rise to the 6,9-imino ether **III**,[1a] which after reduction and N-methylation affords I. In the course of our study on the Beckmann rearrangement of erythromycin A 9(E)-oxime **II**, we found that trapping of the intermediate nitrilium ion with a different neighboring hydroxy group can be achieved by varying the reaction conditions. A recent publication[3] describing a related finding prompts us to report our results.



I azithromycin

When the Beckmann rearrangement of **II** was carried out in ethyl ether in the presence of pyridine and toluenesulfonyl chloride at -45 °C, a novel product, the 9,11-imino ether **IV**, was generated in addition to the known **III** and lactam **V** (Scheme 1).[4] Trapping of the 11-hydroxy group by the nitrilium ion was confirmed by single crystal X-ray structural determination of compound **IV** (Figure 1). It is important to note that low temperature (-45 °C) is essential for producing 9,11-imino ether **IV**. At 0 °C in ethyl ether, the

reaction resulted in the exclusive formation of lactam V, in accord with the observations reported by the Pliva researchers.[1a]

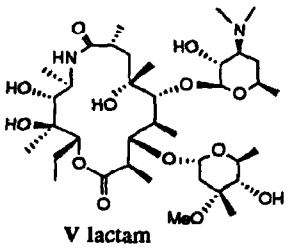


II 9(E)-oxime erythromycin III 6,9-imino ether IV 9,11-imino ether

Reaction Conditions		Ratio of III/IV (yield)
Literature procedure:[1a]	$NaHCO_3$, TsCl, 0 °C, 4 h, acetone-H_2O	100 : 0 (87%)
This work:	Pyridine, TsCl, -45 °C, 6.5 h, ether	44 : 50 (85%)

* *In the product mixture, 6% of lactam V was also present.*

Scheme 1



V lactam

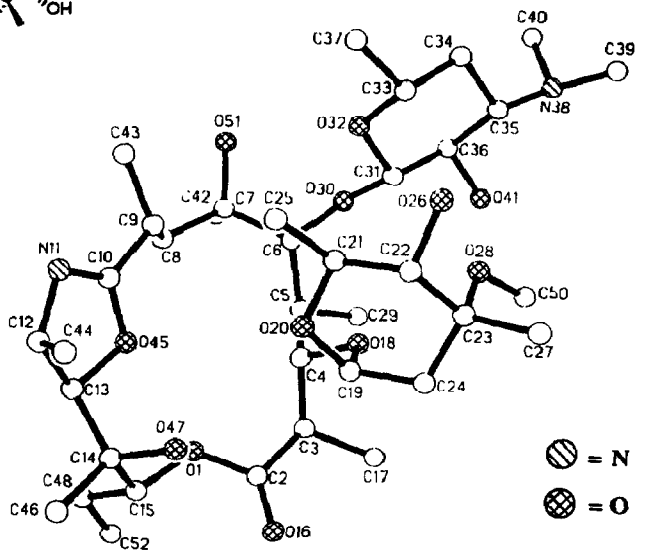


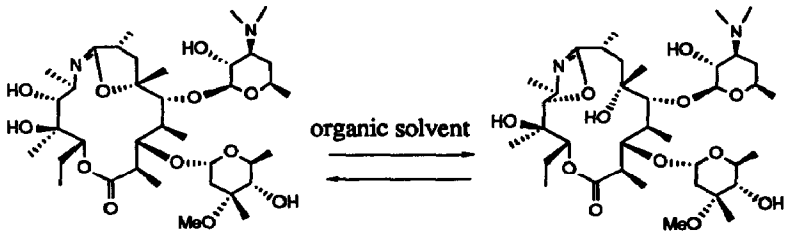
Figure 1. X-ray Crystal Structure of IV

To our surprise, the 6,9-imino ether III readily isomerized to the 9,11-imino ether IV in many organic solvents, despite the fact that crystalline III shows essentially no change over a period of ten years.

In deuterated chloroform, **III** was converted to a 8/92 ratio of **III/IV** over seven days.[5] As shown in Table 1, the **III/IV** ratio is solvent dependent and is shifted by addition of camphorsulfonic acid (CSA). Furthermore, the moisture content in the solvent may also impact the **III/IV** ratio. In the case of anhydrous THF, the 6,9-imino ether **III** was converted to a 90/10 ratio of **III/IV** in 88 hours; adding 2 μl water to a solution of **IV** (25 mg) in 5 ml THF afforded a **III/IV** ratio of 63/37 within the same time period.

Table 1. Ratio of **III/IV** in Organic Solvent in the Presence or Absence of CSA(88 hours)

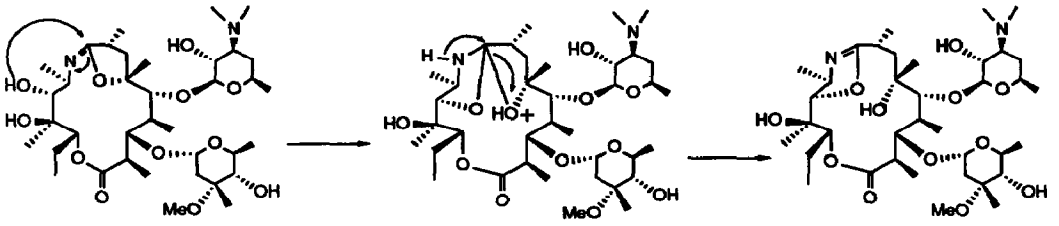
Solvent		Addition of 0.1 equivalent of camphorsulfonic acid
CH_2Cl_2	42/58	27/73
$CHCl_3$	53/47	21/79
THF	90/10	46/54



III 6,9-imino ether **IV** 9,11-imino ether

Scheme 2

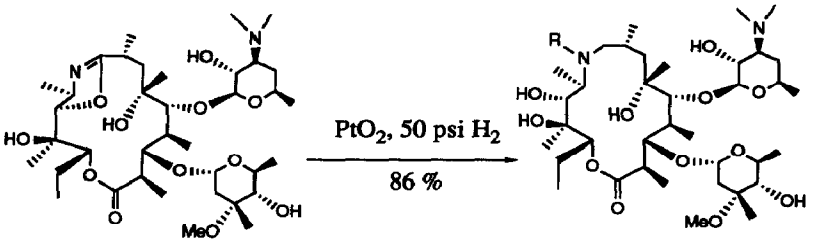
The isomerization is reversible (Scheme 2). For example, 9,11-imino ether **IV** was converted to a mixture of **III** and **IV**, with **III/IV** ratios of 39/61, 11/89 and 9/91 in THF, EtOAc and $CDCl_3$ in 120 hours, respectively. Molecular mechanics calculations using the Tripos force field[6] indicate that the macrolide ring is sufficiently flexible to avoid any steric interactions that would favor one isomer. Instead, since the major structural change involves the imino-ether, the interaction of the local dipole around the imino-ether with the solvent may influence the equilibrium between **III** and **IV**. A proposed mechanism which takes into account a dependence of the **III/IV** ratio on both the polarity and moisture content of the solvent is shown in Scheme 3.



III 6,9-imino ether **IV** 9,11-imino ether

Scheme 3

Finally, 9,11-imino ether IV was converted to azithromycin by using conditions similar to those used in conversion of intermediate III (Scheme 4). However, the hydrogenation was effected under much lower pressure (50 psi H_2, PtO_2, HOAc, 86% yield) in comparison with the literature procedure.[1a] As expected the methylation on the nitrogen proceeded uneventfully.



Scheme 4

Acknowledgment: We are grateful to Jon Bordner for the X-ray crystallographic analysis of compound IV. We also gratefully acknowledge discussions with Dr. John Lowe and Professor Dan Kemp.

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3. Wilkening, R. R.; Ratcliffe, R. W.; Doss, G. A.; *et al. Bioorg. Med. Chem. Lett.* **1993**, *3*, 1287.
4. Spectral data for IV: 9-Deoxo-11-deoxy-9,11-epoxy-9,9a-dihydro-9a-aza-9a-homoerythromycin A mp 200 - 203 °C. **^{1}H-NMR** ($CDCl_3$): 5.03 (s, 1H), 4.81 (dd, J = 10.1, 1.8 Hz, 1H), 4.61 (d, J = 7.3 Hz, 1H), 4.50 (d, J = 4.7 Hz, 1H), 4.39 (d, J = 8.5 Hz, 1H), 4.14 (m, 1H), 3.95 (m, 1H), 3.69 (d, J = 5.9 Hz, 1H), 3.67 (s, 1H), 3.61 (s, 1H), 3.54 (m, 1H), 3.31 (s, 3H), 3.24 (m, 1H), 3.00 (t, J = 9.7 Hz, 1H), 2.70 (m, 1H), 2.68 (m, 1H), 2.66 (m, 1H), 2.25 (s, 6H), 1.97 (s, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.28 (s, 3H), 1.25 (d, J = 6.4 Hz, 3H), 1.22 (s, 3H), 1.21 (S, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.175 (s, 3H), 1.14 (d, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). **^{13}C-NMR** ($CDCl_3$):176.3, 170.1, 102.2, 95.3, 83.0, 82.3, 81.1, 77.7, 76.7, 76.4, 75.1, 73.2, 72.7, 70.7, 69.5, 65.9, 65.1, 63.5, 49.3, 43.4, 40.3, 39.6, 34.6, 29.8, 28.7, 25.0, 24.2, 21.7, 21.66, 21.0, 19.3, 18.1, 17.4, 11.3, 10.9. FABHRMS: m/e 731.4744 (MH^+, $C_{37}H_{67}N_2O_{12}$ requires 731.4694).
5. The ratio of III/IV was determined from the integral of the proton NMR spectrum.
6. Simulated annealing was performed on III and IV using SYBYL 6.0 supplied by Tripos Associates, St. Louis, MO 63144. Gasteiger-Huckel charges were used and the dielectric was set to 5.0 for chloroform.

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